REMARKS

Reconsideration of this application is requested.

The applicant proposes to delete the alternative step (c) from claims 1 and 28 as unnecessary. Additionally, it is proposed to delete claim 5 and a part of claim 4 to avoid redundancy with the last step recited in claim 1.

It is further proposed to correct a spelling error in the last line of claims 1 and 28 (i.e. "eluded" should be "eluted").

The indicated amendments do not raise any new issues. Hence entry of this amendment for allowance or appeal is requested.

The Examiner is requested to reconsider the Section 102(b) rejection of claims 1, 2, 6-8, 10-14, 16-21, 25 and 28 as anticipated by Berglund et al. (U.S. 6,090,288). With respect, it is submitted that the applicant's claims distinguish patentably from Berglund et al.

The Examiner states that

> "Berglund et al. also teach purification of oligonucleotides using an increasing pH gradient without a substantial increase in metal concentration and thus anticipate the instant claims. Berglund et al. teach this as follows.
>
> First, Berglund et al. teach that oligonucleotides can be purified by just increasing of pH (see claim 14 step c). In claim 14, Berglund teaches that elution can be accomplished by any one of three elements alone and by any combination of those three elements by teaching these elements as 'and/or' elements. As one of the elements is elution by salt, Berglund et al. specifically teach that that element need not change, that is, that elution can be accomplished just by increasing the pH alone. Thus the teachings of Berglund anticipate instant claims 1 and 28 steps a and b and step d (an alternative to step c)."

The applicant respectfully submits that the Examiner's interpretation of claim 14 cannot meet the standard required for anticipation of applicant's claims. That elution by salt is claimed by Berglund as an alternative to the use of increasing pH cannot be interpreted as a disclosure of the use of an increasing pH gradient in the absence of a substantial increase in salt concentration. Berglund's claim 14 contains absolutely no disclosure of how the increasing pH gradient is achieved, whether the salt concentrations of the solutions used increase in salt concentration, whether they decrease, or remain the same. Significantly, there is no disclosure of the applicant's requirement that the pH gradient should be increased in a way which avoids the need for subsequent desalting. Claim 14 is completely silent on these matters, and therefore

cannot disclose each and every feature of the rejected claims as required to sustain rejection for anticipation.

The Examiner also states that:

> "Second, Berglund et al. teach that the salt concentration can be decreased when a pH gradient is used (see column 2 lines 33-44), thus further meeting the limitations of instant claims 1 and 28, especially step d."

Here again, however, the Examiner's reference to Berglund's disclosure of the use of a decreasing salt concentration is incorrect. The Examiner references the passage at Col 2, lines 33 to 44. This passage refers to chromatofocusing (line 35). Berglund expressly states that chromatofocusing is not within the scope of the process of the present invention (lines 43-44). Accordingly, this disclosure cannot be read as forming part of the disclosure of conditions which could or should be employed with the remaining features disclosed by Berglund.

The Examiner's assertion that Berglund teaches a pH gradient in the absence of an increase in salt concentration is a complete contradiction of the actual teaching of Berglund which is that elution at pH 9 using the relatively low-salt buffer E is ineffective, and hence the substantially higher salt concentration buffer F is employed for elution at pH 9. This substantive difference from the applicant's invention is more fully discussed in the paragraph bridging pages 6-7 of applicant's response of November 24, 2008 wherein the applicant noted the following:

> "As the Examiner has recognized, Berglund does not disclose or suggest the features of applicant's claims 4 and 5, now part of applicant's independent claims 1 and 28. The key part of the Berglund teaching in this regard is the composition of Buffer F. This is formed by the addition of 2M NaCl to Buffer E. Buffer F, therefore, comprises a substantially higher concentration of metal salts than Buffer A (20mM sodium phosphate). Accordingly, the linear pH gradient teaching of Berglund not only employs a pH gradient, but also a substantial increase in the concentration of metal salts in the elution solution. Significantly, at column 13, lines 29 to 50, Berglund compares the performance of Buffer E (relatively low metal salt concentration) with that of Buffer F for elution at pH 9, the same pH as employed in the linear pH gradient of Experiment 7 referred to by the Examiner. At Column 13, lines 45 to 50, the use of Buffer E is taught to produce a fraction containing contaminants. This problem is directly taught to be overcome by the use of the high-salt Buffer F. The clear teaching of Berglund is that the purification of oligonucleotides using an increasing pH gradient also requires a substantial increase in metal salt concentration. This is exactly the opposite to the applicant's invention as brought out in the amendments to claims 1 and 28."

For the reasons noted, the applicant submits that the Examiner's Section 102(b) rejection of claims 1, 2, 6-8, 10-14, 16-21, 25 and 28 is not warranted and should be withdrawn.

The Examiner has also rejected claim 5 under Section 102(b) as anticipated by Berglund. The applicant does not agree with the Examiner's rejection. However, claim 5 has been cancelled without prejudice in order to reduce the issues. Applicant reserves the right to pursue the substance of claim 5 in a later filing.

The Examiner is respectfully requested to reconsider the several Section 103(a) rejections as set out in Sections 7, 8, 9, 10 and 11 of the action. These rejections are all based on Berglund et al., discussed above, with such secondary references as Bloch (U.S. 5,856,192); Crane et al.; Asteriadis et al., Früchtel et al. and Bambara et al. These references, no matter how considered, do not make the applicant's invention obvious.

Initially applicant notes that the Examiner's position in rejecting the claims under Section 103(a) is not really clear. For example, Section 7 of the action refers specifically to rejection of claims 3-5 and 24 based on Berglund and Bloch. However, in discussing the rejection, the Examiner goes on to refer to Bloch with respect to claims 1-3 and 28 (page 5, 2nd ¶ of action) and he then refers specifically to claims 4 and 5 (top, page 6 of the action). Finally, the Examiner concludes that the "invention as a whole is prima facie obvious over the combined teachings of the prior art", although he also uses this language when referring to claim 9 in isolation.

In any case, the applicant submits that all of his claims define subject matter which is not obvious from Berglund considered with Bloch and/or any of the Examiner's other secondary references. As noted above, Berglund does not teach the use of an increasing pH in the absence of a substantial increase in salt concentration. Indeed, the skilled person, when considering the teaching of Berglund with respect to the inadequate performance of Buffer E, and the need to employ the higher salt concentration buffer F in order to achieve efficient elution, would conclude that Berglund, if anything, was teaching away from the applicant's process as claimed.

With regard to Bloch, this again contains no disclosure of the use of an increasing pH gradient in the absence of a substantial increase in salt concentration. While Bloch refers to isocratic formats at Col 17, line 15, this is expressed as an alternative to pH gradient, and there is no reference at all to an increasing pH gradient. Significantly, the processes exemplified by Bloch all employ constant pH, and involve the use of a significant increase in salt concentration in order to achieve elution. The

teaching of Bloch is therefore entirely consistent with the teaching of Berglund concerning the importance of increasing salt concentration in order to achieve an efficient process. Accordingly, the skilled person would have absolutely no motivation, based on the combined teachings of Bloch and Berglund, to contemplate the use of a process as claimed by the applicant involving the use of an increasing elution pH in the absence of any substantial increase in salt concentration. It is, therefore, submitted that the claims of the present application would not be obvious to the skilled person over the combined teaching of Berglund and Bloch.

The Examiner's other secondary references do not fill in the clear-cut deficiencies of Berglund and Bloch. Thus, Crane discloses an affinity chromatography process using PEI-silica gel. There is no teaching in Crane which overcomes the aforementioned deficiencies in the Examiner's combination of Berglund and Bloch.

Asteriadis does indeed employ ammonium hydroxide. However, this is not in the context of a process as claimed by the applicant. Indeed, Asteriadis employs elution processes which employ substantial increases in salt concentration in order to achieve elution. The teaching of Asteriadis is, therefore, entirely consistent with the teaching of Berglund and Bloch concerning the importance of increasing salt concentration in order to achieve an efficient process. This consistent teaching provides a further illustration of why the skilled person would not contemplate the process of the present invention when considering the teaching of Berglund and Bloch in combination. Indeed, faced with such a consistent message from the prior art, the skilled person would have every reason to go in a direction different from the one the applicant has taken. Thus, if anything, the teaching of Asteriadis strengthens the applicant's position and serves to highlight the inappropriate hindsight employed by the Examiner in his obviousness rejections.

Früchtel contains no teaching concerning the chromatographic purification of oligonucleotides whatsoever, and is solely concerned with solid phase synthetic methods. It takes a remarkable amount of hindsight and very selective picking and choosing to identify any commonality between Früchtel and the teachings of Bloch and Berglund. However, it is well known in the art that trityl protecting groups are acid labile, and that acetic acid is one of the acids that can achieve this deprotection. The applicant does not in any way accept the Examiner's argument that it would be obvious to combine the teaching of Früchtel with Berglund and Bloch to reach the invention.

Bambara cannot fill in the fundamental deficiencies of the other references. Bambara has been extensively discussed in earlier prosecution and clearly does not fill

in the substantive defects of Berglund and Bloch. The applicant has noted the Examiner's argument that a pH of 7.5 is about 8 (which is arguable), but he then goes on to state that a pH of 8.5 is "about 11" (last ¶, page 10 of the action). Surely this is clearly an unsustainable position. Manifestly, a pH of 8.5 (mildly alkaline) is actually closer to acidic pH than it is to pH 11. The error in the Examiner's position is even more evident when it is considered that one is talking about a logarithmic scale, so that the difference of 1 pH unit is actually an order of magnitude in terms of hydrogen ion concentrations. There is absolutely no way that the skilled person would consider a process of increasing pH from 7.5 to 8.5 as approximating to a process where the pH is increased from about 8 to about 11 or that a pH of 8.5 is about pH 11.

For all of the reasons noted above and for the reasons earlier of record, the applicant submits that the claims herein define novel and unobvious subject matter. Accordingly, the claims should be allowed.

Favorable reconsideration is requested.

Respectfully submitted,

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Date: June 22, 2009

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